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EXAMINER
WOITACH, JOSEPH T

ART UNIT	PAPER NUMBER
1632	6

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Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.	Applicant(s)
09/932,521	Herweijer et al.
Examiner	**Art Unit**
Joseph Woitach	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 13, 2003*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-20* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Aug 17, 2001* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This application claims benefit to provisional application 60/225,946 filed August 17, 2000.

Election/Restriction

Applicant's election of group II, filed March 13, 2003, in Paper No. 5 is acknowledged. Upon reconsideration of the restriction requirement, though the particulars of Group II are not required for the practice of groups I or III, it would not constitute an undue burden to search all three groups together as they are directed to process for transgene expression. Therefore, the restriction requirement is withdrawn.

Claims 1-20 are pending and currently under examination..

Information Disclosure Statement

The listing of references in the specification (bridging pages 7-8) is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Objections

Claims 1 and 18 are objected to because of the following informalities: the claims include internal periods in the listing of each of the steps. Each claim must begin with a capital letter and end with a period. See MPEP 608.01(m).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claims 1 and 18 are vague and unclear in the recitation of "expressing the nucleic acid for an extended periods of time" because the metes and bounds of "extended" are indefinite. In one case, extended periods of time can be interpreted as a specific period of time of expression, however what would constitute an extended period of time is not specifically taught in the specification, and constitutes a generic term subject to various interpretations varying from artisan to artisan. The metes and bounds of the claim are subject to various interpretations of what is comprised by the term extended for the specific time of expression encompassed by the claims. Alternatively, the term extended can be interpreted as providing additional time,

however what time which is extended by practicing the claimed method, over practicing the method by another means, is not specifically taught in the present specification. By either interpretation, the metes and bounds of the claims are indefinite because what is encompassed by extended is not clearly set forth in the claim nor specifically defined in the specification. Dependent claims are included in the basis of the rejection because they only set forth structural features of the nucleic acid used in the method without indicating how they may or may not affect the time of expression.

Claims 8, 10 and 12 are vague and unclear in the recitation of "by inside ends derived from Tn5 transposase", "by outside ends derived from Tn5 transposase" and "by chimeric ends derived from Tn5 transposase", respectively. Initially, a transposase is a protein, not a nucleic acid sequence, and it is unclear how one would derive any sequence from a protein which could be used to flank a polynucleotide sequence, i.e. the expression cassette. Further, the specification does not specifically define what the metes and bounds or specifically teach what constitutes the inside, outside or chimeric ends of a Tn5 transposase. It is unclear what specific elements or what specific sequences of a transposase are encompassed by each of the claims because where the inside and outside of a Tn5 transposase start and/or end is not specifically set forth or taught in the specification. With respect to providing chimeric ends, it is unclear specifically what this term encompasses or how different ends can be obtained from a single Tn5 transposase. Dependent claims 9, 11 and 13 are included in the rejection because they fail to further clarify the basis of the rejection.

Claim 18 recites the limitation "the nucleic acid" in the third line. There is insufficient antecedent basis for this limitation in the claim. It is unclear if this is in reference to the expression cassettes or the vector recited previously in the claim or to some other nucleic acid which is generated in step (a). Additionally, the claim is incomplete and unclear because the preamble indicates that the method is directed to transgene expression, however there is no method step for delivery in any form, nor steps indicating if or how expression is affected *in vivo*, *in vitro*, or artificially by some other means. More clearly setting forth method steps indicating where or how transgene expression' occurs would obviate this portion of the rejection. Dependent claims 19 and 20 are included in the rejection because they fail to further clarify the basis of the rejection and only indicate how a linear nucleic acid is generated.

Claims 19 and 20 recite the limitation "the linear nucleic acid" in the first line. There is insufficient antecedent basis for this limitation in the claim. It is unclear if this is in reference to the "linear vector" in step (a) or the "nucleic acid" in step (b). Further, it is unclear if these claims comprise simply a step in the generation of the vector/nucleic acid or indicate the final step for making it linear. For example, it is not clear if the whole construct must be generated by restriction digest or PCR, or if one can use restriction digest or PCR to generate only a portion of the expression cassette to complete the final construct. How and/or when restriction digest or PCR is used with respect to claim 18 is not clearly set forth.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 7, 18 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Wolff *et al.* (Science, 1990).

Claim 1 encompasses delivering a non-viral, linear nucleic acid to a cell in vivo and allowing the nucleic acid to be expressed. As generally known in the art, the specification teaches that nucleic acids include RNA molecules (page 11, lines 7-20) with is a linear non-viral nucleic acid. Wolff *et al.* teach the direct transfer RNA and expression of the encoded gene into mouse muscle. More specifically, Wolff *et al.* teach that RNA can be generated from a plasmid (page 1468, ref 26)(claim 7) and that when injected provided expression of a marker gene for several hours (solid bar in graph in figure 3). Blunt ends, sticky ends and chimeric ends are not specifically defined in the specification, however as they would apply to a single stranded RNA

molecule, a ssRNA has blunted end which because it is single stranded could anneal to other polynucleotides and thus be interpreted as blunt ended and sticky ended nucleic acids. Further, the two ends of the RNA generated, the 5' and 3' ends, are two different sequences so they could be considered chimeric ends. Wolff *et al.* describe the construction of the plasmid used to make the linear RNA, and teach that restriction enzyme digests were used to sub-clone the various fragments (page 1468, ref 12)(claims 18 and 19). Thus, given the breadth and clarity of the pending claims, the teaching of Wolff *et al.* for the generation of RNA and the delivery and expression of said RNA to muscle for *in vivo* expression of a gene anticipates the instantly claimed invention.

Claims 1, 2, 5, 7-13, 18 and 19 are rejected under 35 U.S.C. 102(a) as being anticipated by Goryshin *et al.* (Nature Biotech, 2000) as evidenced by Gibco BRL (page 14-19).

Goryshin *et al.* describe an *in vivo* method using a transposition system to insert exogenous nucleic acid sequences (see summary in abstract). Specifically, Goryshin *et al.* teach that the transposon sequences for Tn5 can be cloned into a plasmid vector and used to insert said vector into endogenous sequences. The vectors used by Goryshin *et al.* are bacterial and contain the selectable marker for antibiotic resistance (page 98, second column and vector construction described, page 99, second column). Goryshin *et al.* teaches that the transposon sequences used are mosaic indicating they are not the same (page 99, middle of second column). Further, Goryshin *et al.* teach to provide functional fragments of the Tn5 to generate a transposome for

use in transposition of vectors and expression of encoded genes and given the lack of clarity for what would constitute an inside or outside end of Tn5, the teaching of Goryshin *et al.* is being interpreted to anticipated these limitations. Before administering the constructs the vectors are cut with PvuII (page 98, Table 1(A) and page 99, second column) which is a restriction enzyme that generates blunt ends (see Gibco as evidence of restriction site). After delivering the vector to the cells, the cells are grown on a selective media containing the antibiotic kan (or G418), wherein the expression of the kanomycin resistance gene of the delivered vector is expressed sufficiently long time to allow for colonies to form (page 98, Table 1(B) and starting at bottom of page 99). Thus, the teaching of Goryshin *et al.* for the generation of blunt ended transposition vectors and the delivery and expression of said vector *in vivo* to bacterial and yeast cells anticipates the instantly claimed invention.

Claims 1, 2, 5, 7-13, 18 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Tucker *et al.* (US Patent 5,102,797, issued 1992) as evidenced by Gibco BRL (page 14-19).

Tucker *et al.* describe an *in vivo* method using a transposition system to insert exogenous nucleic acid sequences into the chromosome of a cell (see summary in abstract). Specifically, Tucker *et al.* teach that the transposon sequences for Tn5 can be cloned into a plasmid vector and used to insert said vector into endogenous sequences of a cell. Tucker *et al.* teach that the vector is "preferably a linear polynucleotide" comprising the Tn5 sequences (column 6, lines 19-25) and that the vector contains a sequence which encodes a marker which can be detected (column 6,

lines 40-52). By way of example, Tucker *et al.* reduce to practice a polynucleotide which encodes a kanamycin resistance gene which is contained between the mosaic ends of a Tn5 transposon (bridging columns 7-8). The plasmid is linearized as well as excised with PvuII and used to transfect cells. The cells are allowed to grow on kanamycin containing media and by expression of the kan^R gene, colonies are formed (see summary in Table 1, column 8). Thus, the teaching of Tucker *et al.* for the generation of blunt ended transposition vectors and the delivery and expression of said vector *in vivo* to cells anticipates the instantly claimed invention.

Claims 1, 16, 17 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Rolland *et al.* (US Patent 6,514,947).

As discussed above, claims 1 and 18 are broad encompassing the delivery of a non-viral linear nucleic acid to a cell and expressing a nucleic acid sequence on said construct. Dependent claims 16 and 17 are directed delivery by intramuscular and interstitial injection. Rolland *et al.* teach a method for the delivery and expression of a nucleic acid vector to an mammal *in vivo* (see summary in abstract and claim 1 for example). More specifically, Rolland *et al.* teach that a nucleic acid vector can be many forms of non-viral nucleic acids including RNA, cDNA and plasmid DNA (column 2, lines 37-40). Furthermore, though it is known in the art that cDNA and RNA are linear nucleic acids, Rolland *et al.* specifically teach that whatever vector used can be provided in a linear form (column 2, lines 58-59). Rolland *et al.* teach that the vector can comprise one or more genes to be expressed (column 2, lines 58-59), and by way of example a

reduction to practice using the expression and detection of the luciferase and CAT transgenes is provided (see figures 6 and 8, on sheet 5 of 8). Finally, Rolland *et al.* teach that various routes of delivery can be used including within the muscle or interstitial space of a joint (column 2, lines 30-33 and claims 5 and 8). Thus, the teaching of Rolland *et al.* for the generation linear non-viral nucleic acid vectors and the delivery and expression of said vector *in vivo* by intramuscular and interstitial injection anticipates the instantly claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 7, 14, 15, 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rolland *et al.* (US Patent 6,514,947) in view of Budker *et al.* (Gene Therapy, 5:272-276, 1998).

Claims 1 and 18 encompass the delivery of a non-viral linear nucleic acid to a cell and expressing a nucleic acid sequence on said construct. Dependent claim 7 recites that the expression cassette is isolated from a plasmid backbone and claim 19 encompasses the nucleic acid prepared by restriction enzyme digest, and claims 14 and 15 are directed delivery by intravascular injection, in particular wherein pressure is used in the delivery. As summarized above, Rolland *et al.* teach a method for the delivery and expression of a nucleic acid vector to an mammal *in vivo* (see summary in abstract and claim 1 for example). More specifically, Rolland *et al.* teach that a nucleic acid vector can be many forms of non-viral nucleic acids including RNA, cDNA and plasmid DNA (column 2, lines 37-40). Furthermore, though it is known in the art that cDNA and RNA are linear nucleic acids, Rolland *et al.* specifically teach that whatever vector used can be provided in a linear form (column 2, lines 58-59). Rolland *et al.* teach that the vector can comprise one or more genes to be expressed (column 2, lines 58-59), and by way of example a reduction to practice using the expression and detection of the luciferase and CAT transgenes is provided (see figures 6 and 8, on sheet 5 of 8). Finally, Rolland *et al.* teach that various routes of delivery can be used highlighting several routes known and used in the art (column 2, lines 30-33). In summary, Rolland *et al.* teach the generation linear non-viral nucleic acid vectors and the delivery and expression of said vector *in vivo.* However, while Rolland *et al.* teach that various routes of administration can be used they do not specifically teach to the methods for intravascular delivery. At the time of filing various routes of administration of polynucleotides were known beyond those specifically used and disclosed by Rolland *et al.*

Budker *et al.* teach a method for the efficient expression of a transgene in muscle cells of a rat using intravascular delivery (claim 14) of a non-viral nucleic acid wherein increased hydrostatic pressure is used to deliver the vector (see summaries on page 272 in second paragraph in the first column and final two paragraphs on page 276)(claim 15). Additionally, the lacZ gene expression cassette used and expressed in the delivery methods described in Budker *et al.* was obtained as a restriction fragment from the plasmid pBS-RSV-LacZ and inserted into pCI (see figure 4)(claims 7 and 19). Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the delivery methods specifically taught by Budker *et al.* in the methods generally described by Rolland *et al.* One having ordinary skill in the art would have been motivated to use the methods of Budker *et al.* because they represent an efficient means of delivery and offers the specific guidance for the delivery of polynucleotides to cells and/or tissues not easily obtained by the methods specifically described by Rolland *et al.* There would have been a reasonable expectation of success given the successful results demonstrated by both Rolland *et al.* and Budker *et al.* demonstrating the ability of delivering a non-viral nucleic acid to a cell *in vivo* and obtaining expression in said cells by various routes.

Thus, the claimed invention of delivering a non-viral nucleic acid to cell in vivo by intravascular injection as a whole was clearly *prima facie* obvious.

Claims 1, 6, 18 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tucker *et al.* (US Patent 5,102,797) in view of Sambrook et al. (Molecular Cloning, Vol 2, section 14.5, 1989).

Claims 1 and 18 encompass the delivery of a non-viral linear nucleic acid to a cell and expressing a nucleic acid sequence on said construct. Dependent claims 6 and 20 recite that the nucleic acid is generated by polymerase chain reaction. As summarized above, Tucker *et al.* describe an *in vivo* method using a transposition system to insert exogenous nucleic acid sequences into the chromosome of a cell (see summary in abstract). Briefly, Tucker *et al.* teach that the transposon sequences for Tn5 can be cloned into a vector and used to insert said vector into endogenous sequences of a cell. As an example, Tucker *et al.* provide a detailed example for the production of specific nucleic acid vector (figures 1-3). Moreover, Tucker *et al.* teach that the vector is "preferably a linear polynucleotide" (column 6, lines 19-25) and that the vector contains a sequence which encodes a marker which can be detected (column 6, lines 40-52). In a reduction to practice, Tucker *et al.* teach that the plasmid is linearized and the expression cassette is excised with the restriction enzyme PvuII, and the linear nucleic acid is used to transfect cells. Tucker *et al.* specifically teach that one can obtain a linear expression construct through the use of restriction enzymes however, Tucker *et al.* does not teach other general molecular methods for obtaining linear fragments of a nucleic acid sequence. At the time of filing Sambrook *et al.* teach that PCR amplification results in linear fragments of DNA which can be used for many molecular applications including molecular cloning (section 14.5). Therefore, it would have

been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the PCR methods taught by Sambrook *et al.* to generate the vector fragments or provide the final linear fragment used in the delivery methods specifically taught by Tucker *et al.* One having ordinary skill in the art would have been motivated to use the methods of Sambrook *et al.* because they represent an efficient means of obtaining large amounts of linear fragments of DNA and specific sequences from various plasmids that are not easily obtained by the methods of restriction digest. There would have been a reasonable expectation of success to use PCR to generate linear nucleic acids because the method of PCR results in linear fragments, and the molecular techniques of cloning fragments using PCR are conventional.

Thus, the claimed invention of delivering a linear non-viral nucleic acid made by PCR to a cell *in vivo* as a whole was clearly *prima facie* obvious.

The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure.

Reznikoff *et al.* (US Patent 6,159,736 and 5,948,622) teach a non-viral vector comprising Tn5 elements which is used in a method to transpose the nucleic acid into a cell. Similar to the teachings of Tucker *et al.* discussed above, Reznikoff *et al.* provides guidance for the use of Tn5 containing vectors to deliver expression vectors to cells in culture.

Cox *et al.* (US Patent 6,140,129) teach that other various recombinases can be combined onto one vector for use in methods in which exogenous polynucleotides are delivered to a cell. In particular, Cox *et al.* teach that Tn5 and FRT recombinase elements can be used in a vector system to obtain targeted insertion of a sequence of interest.

Budker *et al.* (Gene therapy 3:593-598, 1996) and Herweijer et al. (Molecular Therapeutics 1(7):504-509). Each teach the delivery of non-viral, non-linear plasmid DNA for the expression of a transgene *in vivo*. Similar to the teachings of Budker *et al.* discussed above, each reference provides evidence that at the time of filing that naked polynucleotides were being delivered IM and IV.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach

Joe Woitach

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